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DIABETES MELLITUS: DEFINITION AND PATHOLOGY

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"In the papyrus Ebers, which is a copy of an Egyptian medical compilation already old in the time of Moses, there is mention of polyuria, and it is hard to conceive that such a marked departure from health could at any time have escaped observation." (Saunby.)

However ancient may be the recognition of this departure from health, there are still many missing links in the chain that will finally make the subject of diabetes from every standpoint complete. It is well to consider briefly the normal physiology of digestion, especially that of the carbohydrates, in order to get a clear definition of the disease known as diabetes mellitus.

A diet sufficient to maintain growth and sustain body economy must contain protein, fats, carbohydrates, inorganic salts, water and vitamines, the latter in quantities sufficient to prevent such nutritional diseases as beri beri, pellagra, scurvy and rickets. Chemically, vitamines are known as fat-soluble A, water-soluble B, and the antiscorbutic vitamine. A detailed discussion of vitamines is not, at this point, essential to our subject, but the digestion and the relationship to each other and to body economy of the proteins, fats and carbohydrates require very careful consideration. On reaching the stomach, the protein molecule is acted on by the hydrochloric acid and the pepsin of the gastric juice and is split into other substances known as proteoses and peptones. These products when passed into the duodenum are broken down by the intestinal enzymes, principally the trypsin of the pancreatic secretion, into the amino acids which are the ultimate building stones of the body. These amino acids are absorbed and carried by the blood to the organs and tissues and they are used for the reconstruction of the broken down protein. Any excess of the amino acids, along with that liberated in the tissues by disintegration of tissue protein, is split into two portions, one represented by ammonia and the other by the remainder of the amino acid molecule. The former is excreted as urea, the latter is oxidized to produce energy. The average requirement of protein in the normal diet should approximately be one to one and one-half grams per kilogram of body weight, or about 100 grams in 24 hours. Growing children and elderly people need more protein than middle aged people. There will be occasion to refer to protein metabolism later.

The next dietary element to consider is fat, its digestion and utilization. Neutral fats are split into fatty acids and glycerin by a lipolytic enzyme present in the pancreatic juice called lipase, assisted by the bile. The bile salts are the constituents of the bile that activate the lipase and in addition the bile aids the digestion of fat by containing an alkali and mucin-like substance which assists in the emulsification of fats. After the digestion and absorption of fat, it is carried to three places: (1) depots for fat, the subcutaneous and retroperitoneal tissues; (2) liver; (3) tissues. The function of depot fat is familiar to all, namely, its utilization in response to special tissue demand, for example, in starvation the depot fat supplies 90 per cent of the energy which maintains the existence of the animal organism. It is important to keep this fact in mind when diabetes is discussed, for fat is the mother substance of the acid bodies, diacetic acid and acetone that cause the most serious complication of diabetes—acidosis. The fat intake in a healthy individual averages about 100 grams daily.

Protein is necessary to repair tissue waste; fat is stored for emergencies. The carbohydrates are necessary as the most readily available and the most easily combustible fuel for the body. All carbohydrates in the diet are reduced by the action of the enzymes from the complex polysaccharides (if they be so ingested) into the simplest sugars or monosaccharides, such as glucose and levulose, and are absorbed in the portal system as such. The first ferment used in digestion of starches is the ptyalin of the saliva. It is not a very powerful ferment and can act only on the starches that are not surrounded by cellulose. Therefore, the free starches that come in contact with the saliva are swallowed and when they encounter the increase in the hydrogen ion concentration of the stomach contents, due to the existence of hydrochloric acid in the free state, the ptyalin is activated. The product of ptyalin digestion is maltose, a disaccharide. The carbohydrates on leaving the stomach consist of the following: (1) undigested starch, (2) glucose, (3) maltose.

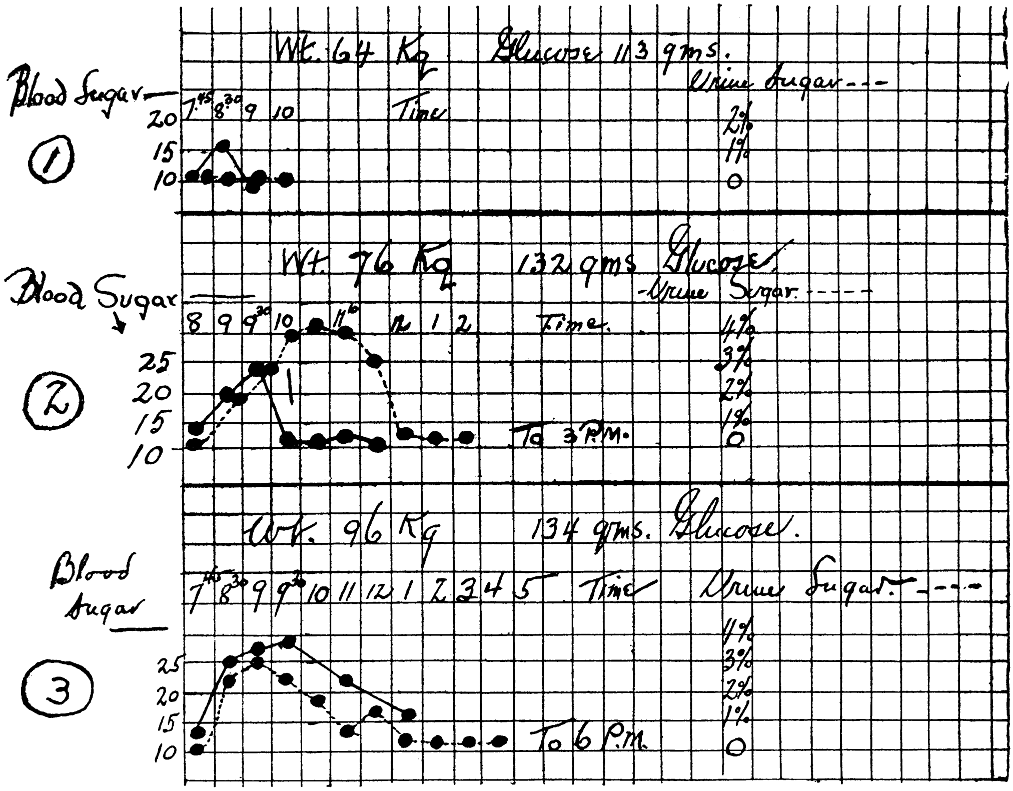
In the duodenum there is a powerful diastatic enzyme called amylopsin that originates in the pancreas and flows from the pancreas by way of the pancreatic duct. Amylopsin quickly hydrolyzes the starch through dextrin into maltose. For each of the disaccharides there exists in the intestinal juice a group of ferments called the inverting enzymes. Maltose, a disaccharide, is converted into two molecules of glucose, a monosaccharide, by the enzyme maltase; lactose is converted into galactose; and glucose by lactase and cane sugar is converted into levulose and glucose by invertase.

In animals whose diet does not contain one of the disaccharides, the inverting enzyme is absent. In addition to the above, bacterial digestion also takes place in the intestine, for example, the splitting of a monosaccharide into fatty acids and gases such as methane, also the digestion of cellulose which is untouched by the ferments. Bacterial digestion is most common in herbiverous animals. The end products of carbohydrate digestion are the monosaccharides, glucose and levulose. These are absorbed into the blood by the portal system.

Digestion up to this point goes on in a diabetic just as efficiently as in a non-diabetic. In other words, the enzyme action of the gastric and intestinal juices in diabetes is the same as in normal individuals. The differentiation between the two lies in the inability of the diabetic organism to utilize the end products of carbohydrate digestion, glucose and levulose, after absorption. This fact I hope to present as succinctly as possible in spite of the numerous hypotheses that relate to it. Though it will be impossible to discuss in detail all these hypotheses, brief mention of the following should be made as a basis for further consideration: (1) There exists a barrier in the non-diabetic individual between the portal circulation and the systemic circulation. You will recall that glucose and levulose are absorbed by the portal blood. Glucose is carried to the liver and muscles which act as warehouses for excess glucose, in which it is converted into and stored as glycogen. The normal blood sugar content is .10 to .11 grams per cent and it is the function of these warehouses to automatically discharge the glycogen which is reconverted into glucose and to maintain this constant blood sugar level. After the digestion of a meal rich in carbohydrates, the excess glucose does not get beyond the barriers, the liver and muscles, in normal individuals, but it is stored in them for body use as glycogen which is reconverted into glucose as it is demanded for body energy and for maintenance of a constant blood sugar level. It must not be overlooked, however, that the ingestion of a meal excessive in carbohydrates, for example cane sugar, may produce in a healthy individual a glycosuria, but not the kind of a glycosuria we find present in diabetics. In diabetes the glycosuria is due to the presence of glucose in the urine regardless of the kind of carbohydrates that is ingested. In alimentary glycosuria in a healthy individual, there appears in the urine an unchanged disccharide similar to the kind ingested (cane sugar), showing that it was taken in amounts too large for the enzymes to split up into the monosaccharides and for the inverting enzymes to properly function upon.

To the non-diabetic individual as compared with the diabetic individual, Allen's paradoxical law applies—"Whereas in normal individuals the more sugar given the more is utilized, the reverse is true in diabetes." Allen shows that the limit of tolerance in non-diabetic animals are all apparent, not real. No real limit of power of utilization of sugar normally exists. This law applies to all species of animals which have been tested, to all methods of administering sugar, and to all sugars and carbohydrates, provided they are utilized at all. This paradoxical law regarding dextrose sharply distinguishes diabetic animals from every type of non-diabetic animal. In diabetic animals the limits of tolerance are real and not apparent. In totally diabetic animals the injection of dextrose causes an excretion of glucose not only equal to, but frequently greater than the doses injected. In milder diabetics, not only is the proportion of excretion to ingestion generally high, but the power of assimilation may be made worse instead of better by an overdose. This paradoxical law enables distinctions to be drawn between true diabetes and glycosuria of other types, whether organic or functional. In every form of non-diabetic glycosuria, the power of utilizing dextrose in amounts increasing with the dose, is retained. You will note the distinction between the utilization and digestion of carbohydrates. In true or potential diabetics, on the other hand, by eliminating the element of digestion by giving a monosaccharide, such as glucose, by mouth, either administering a certain amount per kilogram of body weight or by giving a total of 100 grams, (that is, by applying the technic known as the glucose tolerance test), there appears a hyperglycaemia or increase in blood sugar, to be followed by a glycosuria. The inference is drawn that the sugar retaining powers of the liver and muscles are not sufficiently developed to prevent the accumulation of some of the absorbed blood sugar in the systemic blood. Therefore the existence of a postprandial hyperglycaemia, as revealed by the present day method of examining sugar in the blood, makes it possible to detect early deficiencies of carbohydrate metabolism. Aside from tuberculosis and cancer, early recognition is of no greater importance in any disease than in diabetes. It is recognized that in chronic nephritis, resulting in damage to the kidneys and in long standing diabetes, there may be a higher percentage of blood sugar without glycosuria than is usually the case, therefore the examination of the blood is the only accurate means of detecting such disturbances in metabolism except possibly in acute cases. (See Chart.)

In case No. 1, which is an absolute normal, you will note from the chart of the glucose tolerance test, that there was a rapid rise and fall in the blood sugar and there was no sugar in the urine. In cases Nos. 2 and 3, although there were none of the symptoms of diabetes, such as polyuria, polyphagia and polydipsia, a disturbance in carbohydrate metabolism is suspected. The charts are shown to illustrate how an early faulty carbohydrate metabolism may be detected. You



will note in case 2 the prolonged interval before the return to the base line of both the blood and urine sugar.

In an understanding of the significance of the glucose tolerance test and postprandial hyperglycaemia, note that the question of time as well as the appearance of hyperglycaemia and glycosuria is important. The time of onset of hyperglycaemia after the ingestion of glucose and the extent and duration of the hyperglycaemia are the conclusive points as to the extent of the disturbance. It is almost certain that the first sign of diabetes is an unusual degree and duration of postprandial hyperglycaemia (MacLeod). Up to this point we have traced carbohydrates from their entrance into the stomach to their disposition after absorption by the portal blood, at the barriers, the liver and muscles. There the glucose is changed back into a polysaccharide, glycogen, and is there stored. This brings us to the actual definition of diabetes. In diabetes there is a failure of the animal organisms to store glycogen from the glucose of the portal blood in its warehouse, and furthermore to oxidize and split the glucose in the systemic blood to produce energy. Thus we get a constant rise in blood sugar known as hyperglycaemia and a subsequent glycosuria. You will recall that in the body economy, the carbohydrates are the most available source of body energy, and now you are confronted with a condition that is marked by failure to utilize this source of energy either in part, in mild diabetes, or in toto in severe diabetes. The result is, therefore, a marked upset in the balance of the metabolism. The proteins and fats must be called upon to provide the necessary balance for nutrition.

The actual signs and symptoms of diabetes, clinically, you are familiar with and I will pass over these in order to discuss the pathology more in detail.

It has been proven experimentally that there exists in the blood a ferment called glycogenase, the function of which is to convert the stored glycogen into glucose as the body needs it, and you will recall that the body needs a constant blood sugar level of .10 to .11 grams per cent. There must also exist a substance inhibitive to this ferment in health, otherwise the glycogenase would run riot and discharge and convert all the glycogen from the liver and muscles into glucose or, even worse, prevent the conversion of glucose into glycogen. Possibly in diabetes this actually occurs, with the result that owing to the prevention of the storage of glycogen, the systemic blood containing practically as much glucose as the portal blood, produces not only high blood sugar readings, but also glycosuria. This, then, is what is thought to be the case in diabetes. There is an absence of an inhibiting substance opposed in action to glycogenase, for in diabetes, depending quantitatively upon the severity of the condition, glucose is neither properly stored nor burned. To prove the origin and character of this inhibiting substance is the chief problem in clarifying the pathology of diabetes. Much interesting work has been done to account for this glycogenolysis or the excessive breaking down of glycogen, but results are not yet conclusive. You will recall that in health there is maintained a constant blood sugar level and in diabetes this does not exist. The question arises, how can this constant blood sugar level be maintained in health? It can be done in two ways. First, by means of a nervous reflex mechanism; second, by the existence of some special exciting hormone. Perhaps the presence of the one may be necessary for the functioning of the other. As an example, electrical stimulation of the splanchnic nerve produces a hyperglycaemia through stimulation of the efferent nerves, also puncture of the diabetic center in the medulla produces the same effect, but if the adrenal glands are removed this phenomenon is absent, therefore it has been thought that the adrenal glands must contain such a hormone as we are considering, but it is possible to get an epinepherine hyperglycaemia just as it is to get a thyroid hyperglycaemia without the actual presence of diabetes, but that adrenal secretion is necessary for glycogenolysis is not disputed. The conclusion, however, seems justified that glycogenic function is subject to nervous hormone control. Hyperthyroidism, with its associated increase in metabolism and its sensitiveness to adrenalin even though associated with hyperglycaemia and glycosuria, does not present the picture of permanent diabetes.

In true diabetes, there is furthermore an effort at a new formation of glucose in an attempt to compensate for the disturbance. As an example, glucose in true diabetes is manufactured from the protein molecule. Animals treated with phloridzin excrete all the carbohydrate which is administered to them. If an animal so treated is starved until all stored glucose has been eliminated, it will still continue to excrete glucose. It has been proved that this glucose does not come from the fat, but must come from the protein of the body. Studies of the dextrose (glucose) and nitrogen relationship in the urine, known as observations of the dextrose: nitrogen ratio are used in estimating the degree of severity of serious cases of diabetes. Extremely severe cases—absolute diabetics—present evidence of this conversion of the body protein into glycol aldehyde, glycerol and lactic acid, which are then further converted into glucose.

To return to the consideration of hormones, it is possible that certain ductless glands such as the pancreas, the adrenals, the thyroid, the para-thyroids or pituitary, by virtue of their internal secretions strongly influencing sympathetic nervous control, may bear a relation to diabetes. If so, the mode and type of action remain to be demonstrated.

Allen in the last few years has cleared up many obscure points in regard to the actual experimental production of diabetes and its treatment by removing parts of the pancreas containing the islets of Langerhans. He has been able to produce diabetes experimentally in dogs, and the work of Winternitz, Opie, Cecil, and others has, in a large majority of cases of diabetes that have come to autopsy, demonstrated pathological changes in these islets. In some instances there has been a definite hyalinization of the islets, in others the evaculization of the cells of the islets. The weight of evidence to-day suggests that the primary pathology of diabetes mellitus is in the pancreas, specifically in the cells of the islets of Langerhans. To show sufficient proof to permit the conclusion that these cells furnish the missing hormone whose function provides for the proper storage and oxidization of glucose either directly through an internal secretion or in combination with the secretions of the other ductless glands is not, however, now possible.

Further evidence of pancreatic disease as the cause of glycosuria presented itself in this clinic a short time ago. A robust healthy laboring man, 40 years of age, was admitted to the clinic complaining of severe epigastric pain of few days' duration. Death resulted before there was opportunity for complete study, but the fact that there was a glycosuria was noted. At autopsy there was a complete fat necrosis of the pancrea due to the back flow into the pancreas from the common duct obstructed by a gall stone lodging in the ampulla of Vater. The microscopic sections of the pancreas showed that necrosis extended into the islets of Langerhans in this instance.

In the treatment of diabetes Allen lays down one essential principle which has been followed with satisfactory results in this clinic for six years. The underlying principle of treatment is as follows: Assuming that we have an organ which is incapable of performing its full function, we must give this organ only the amount of work that it can do, therefore, the tolerance for carbohydrates in each individual case of diabetes must be worked out and we must not overburden the pancreas with too much of a load, for there is a downward tendency in tolerance when the pancreas is overloaded. Cases of diabetes should not be discharged with one or two per cent sugar in the urine, as was formerly done, but they should be kept sugar free with as normal a blood sugar as possible and the urine should be kept free from ketone bodies (acetone and di-acetic acid). The dietary deficiency in carbohydrates may be made up to a certain extent by the addition of fat, but it must be borne in mind that for the complete oxidation of fat, the oxidization of carbohydrates is necessary. In other words, a large intake of fat, exceeding the intake of carbohydrates, results in a smudge instead of a bright burning fire. The smoke from the smudge, if I may be allowed to make this comparison, constitutes the abnormal products of the fats which produce the most serious complication in diabetes,—acidosis.

To sum up, the final principle guiding treatment,—a sugar free urine, a blood sugar level of .10 to .11 grams per cent, and the absence of the aceto-acetic ring in the urine. In order to produce this combination which is, of course, the ideal, the patients in many instances cannot be allowed the desired 25 calories per kilogram of body weight, nevertheless, it is surprising in following cases on low diets to observe how well they tolerate them. To do entire justice to the patients, active coöperation must be established between the physician and patient. Patients must be taught their tolerance and the importance of keeping the urine sugar free, as well as the methods for determining sugar in the urine and the requisite dietary variations. Great emphasis should be placed on the necessity of building up in the patient a morale which will suitably equip him to undertake with enthusiasm and resoluteness the battle which lies before him.

Joslin—Treatment of Diabetes Mellitus. Lea & Febiger, Philadelphia, Pa.

Macleod—Physiology and Biochemistry in Modern Medicine. C. V. Mosby Co., St. Louis, Mo.

Allen—Glycosuria and Diabetes. Harvard University Press, Cambridge, Mass.

M. C. Winternitz—Hyaline Degeneration of the Glands of Langehans. Johns Hopkins Hospital Reports, Vol. XVIII, Fascic. 1.

THREE CASES: THE MONEY TEST

By Agnes James, R.N., and Katharine James

Cincinnati, Ohio

"Since you," I said to Mary some weeks later, "seem to be developing into a specialist in emotional disorders, it behooves me to get into a line that promises some sort of interest. I haven't had anything for weeks now, but a procession of 'Little Lord Fauntleroys' with adenoids."

"That's surgery," said Mary severely, "and just what you chose, and I don't see how you can accuse me of specializing in emotion; my last call was an obstetrical case."

"Well, you wouldn't say emotion was absent, would you?"

"Not exactly," she giggled, "I think the father felt quite a bit,—it was twins."

"Horrors! I hope they paid you treble."

"No, they didn't do that, but they did call the girl Mary and the boy Penley, as a graceful acknowledgment of my services."

"That didn't cost them anything, anyway," I said. "What's little Penley's second name?"

"Poppapoulos—Greek, of course."

"Well, it might be worse! He'll probably have a nice nose and by the time he grows up they'll have a hyphen or call themselves something else, or both—the Pope-Poules, perhaps."

"Yes," she said gravely, "at the rate they were getting rich, they're due to be rather awful members of society in another ten years."

"Please God I'm not nursing," I said fervently, "or I'll be sure to get them."